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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/303,232	04/30/1999	MARTIN ADAMCZEWSKI	MO-5176/LEA3	8055

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EXAMINER	
SCHNIZER, RICHARD A	
ART UNIT	PAPER NUMBER
1635	19

DATE MAILED: 05/21/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/303,232	ADAMCZEWSKI ET AL.	
	Examiner	Art Unit	
	Richard Schnizer	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 February 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7,10,22-31 and 34-36* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *35* is/are allowed.

6)☒ Claim(s) *1-7,10,22-31,34 and 36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

An amendment was received and entered as Paper No. 28 on 2/27/02, with a certificate of mailing of 2/1/02. New claims 34-36 were added as requested. Claims 1-7, 10, 22-31, and 34-36 are pending and under consideration in this Office Action.

Continued Prosecution Application

The request filed on 6/4/01 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09/303,232 is acceptable and a CPA has been established. An action on the CPA follows.

A preliminary amendment was received and entered as Paper No. 24 on 6/4/01. Claims 8, 9,11-20, 32, and 33 were canceled as requested. Claims 1-7, 10 and 22-31 remain pending and are under consideration in this Office Action.

The Declaration of Dr. Adamczewski was received and entered as Paper No. 21 on 6/4/01. The Declaration has been fully considered, and is sufficient to overcome the rejection of claims 1-7, 10, and 22-31 for lack of enablement, as set forth in Paper No. 13. However, new grounds of rejection under 35 USC 112, first paragraph are set forth below.

Claim Objections

It is noted that all claims are drawn to a nucleic acid which contains bases 372-2681 of SEQ ID NO:1, bases 335-1822 of SEQ ID NO:3, and bases 95-1597 of SEQ ID NO:5. In other words, embodiment (a) of the claims requires the presence of all three of these sequences because the sequences are not recited in the alternative. If Applicant wishes to claim these sequences in the alternative, the word "or" should be substituted for the word "and" immediately prior to "nucleotide No. 95 to nucleotide No. 1597 of SEQ ID NO:5, in claims 1 and 35.

Claim 10 is objected to because it requires "culturing a vector", which is not a term of art. Generally, one of ordinary skill in the art speaks of culturing cells comprising a vector. It is suggested that step (a) should be amended to require "culturing a prokaryotic or eukaryotic cell containing a vector comprising at least on nucleic acid of claim 1, wherein the nucleic acid is functionally linked to regulatory sequences which ensure expression of the nucleic acid, wherein the culture conditions allow expression of the encoded polypeptide or polypeptides, " etc.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Written Description

Claims 1-7, 10, 22-31 and 34 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to

reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, for the reasons of record in Paper No. 25.

The claims are drawn to nucleic acids that encode a complete or partial insect acetylcholine receptor subunit having the ability to form homooligomeric acetylcholine receptors when expressed in host cells. In embodiment (b) of the claims, the claimed genus encompasses nucleic acids which hybridize to specific subsequences from SEQ ID NOS: 1, 3, or 5 under certain conditions. The subsequences correspond to the open reading frames encoding the homooligomeric receptors, and are bases 372-2681 of SEQ ID NO:1, bases 335-1822 of SEQ ID NO:3, and bases 95-1597 of SEQ ID NO:5. A sequence search performed by the PTO indicates that these subsequences of SEQ ID NOS: 1, 3, and 5 display substantial variability with respect to each other. The subsequence of SEQ ID NO:1 is about 22% identical to the subsequence of SEQ ID NO:3, and about 27% identical to that of SEQ ID NO: 5, whereas the subsequences of SEQ ID NOS: 3 and 5 are about 38% identical to each other. See sequence alignments attached to Paper No. 25.

The following analysis is based on the Guidelines on Written Description published at FR 66(4) 1099-1111 (January 5, 2001) (also available at www.uspto.gov). The following passage on the treatment of genus claims is particularly relevant.

> The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed

correlation between structure and function, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus.

The first question for consideration is whether the reduction to practice of three species of functional homooligomeric insect acetylcholine receptor subunit nucleic acids is sufficient to satisfy the description requirement. The three described species display substantial variability as noted above, indicating that there is substantial variation in the genus. In fact, a search by the PTO found that nucleic acids encoding mammalian homooligomeric alpha 7 acetylcholine receptors showed a similar level of identity to the disclosed insect sequences as the insect sequences did to each other. For example, a nucleic acid encoding a mouse alpha 7 acetylcholine receptor subunit is about 28% identical to bases 335-1822 of SEQ ID NO:3, whereas bases 372-2681 of SEQ ID NO:1 are only 22% identical to this subsequence of SEQ ID NO:3. Further, a nucleic acid encoding a human alpha 7 acetylcholine receptor subunit is about 25% identical to bases 95-1597 of SEQ ID NO:5, compared to the 27% identity between the subsequences of SEQ ID NOS: 1 and 5. See sequence alignments attached to Paper No. 25. Because the degree in variability between the claimed insect sequences is large, and is similar to the variability between insect sequences and mammalian sequences, the reduction to practice of SEQ ID NOS: 1, 3, and 5 is insufficient to adequately describe the genus of functional insect homooligomeric acetylcholine receptors.

Next it must be determined if Applicant has disclosed any relevant identifying characteristics of the genus. Although SEQ ID NOS:1, 3, and 5 all encode polypeptides sharing a common activity, neither the specification nor the prior art teaches any specific correlation

between any physical structure of the nucleic acids and the ability of the encoded products to form complete or partial insect homooligomeric acetylcholine receptors. Thus it is unknown what common structural features allow a nucleic acid to encode a protein with the function of an insect homooligomeric acetylcholine receptor, although it is apparent that substantial structural variation may occur within the broad genus of nucleic acids encoding these receptors as indicated by the low degree of sequence identity between SEQ ID NOS: 1, 3, and 5. One might argue that the encoded proteins show a reasonable degree of amino acid sequence similarity, however in the absence of any disclosure of what particular sequences are required to fulfill the critical requirement of encoding complete or partial functional homooligomeric insect acetylcholine receptors, there can be no disclosure of any structure/function correlation which provides an adequate written description of the claimed genus.

This rejection may be overcome by deleting from the claims embodiment (b).

Response to Arguments

Applicant's arguments filed 2/27/02 have been fully considered but they are not persuasive.

Applicant's arguments at pages 5 and 6 of the response that SEQ ID NOS: 1, 3, and 5 are members of the same genus is persuasive, but this is insufficient to overcome the rejection in view of the variability between these sequences when compared with non-insect homooligomeric acetylcholine receptor nucleic acids. Applicant argues that this variability is not as great as

portrayed by the PTO because the level of identity between subsequences corresponding to bases 1295-2195 of SEQ ID NO:1, bases 432 to 1318 of SEQ ID NO: 3, and bases 154 to 1123 of SEQ ID NO: 5 is much greater than that obtained when comparing their entire sequences. This is unpersuasive because the claims are not limited to these subsequences, rather the claims are drawn to much longer subsequences as discussed above.

Applicant argues at pages 5 and 6 of the response that bases 1295-2195 of SEQ ID NO:1, bases 432 to 1318 of SEQ ID NO: 3, and bases 154 to 1123 of SEQ ID NO: 5 must encode important regions of the claimed receptors because they are highly conserved. This is unpersuasive because the specification fails to show that these, or any other sequences provide the functional characteristics which distinguish an insect homooligomeric acetylcholine receptor from any other homooligomeric acetylcholine receptor. Furthermore, these subsequences are only about 70% identical, and the specification fails to teach which variations in these regions are permissible and which are not. In other words, the specification fails to teach which sequences, other than those comprised by SEQ ID NOS: 1, 3, and 5, will encode functional insect homooligomeric acetylcholine receptors and which will encode loss of function mutants.

Applicant argues at page 6 of the response that, contrary to the position of the PTO, the specification does teach specific correlation between physical structure of the nucleic acid and the ability of the encoded product to form a complete or partial homooligomeric receptor. Applicant relies for support on pages 1 and 2 of the specification which teach that typically sequences of functionally homologous acetylcholine receptor subunits from different animal

species are more closely related than functionally non-equivalent subunits from the same species. This is unpersuasive because, although the art teaches general structural features of acetylcholine receptors, such as transmembrane segments and ligand binding sites, the specification fails to teach any correlation between structure and function which distinguishes functional insect homooligomeric acetylcholine receptors from non-functional insect homooligomeric acetylcholine receptors, or from non-insect homooligomeric acetylcholine receptors. In attachment 1 of the response, Applicant sets forth an analysis of similarity of a variety of acetylcholine receptor subunits. The analysis is summarized in a dendrogram which shows that subsequences of SEQ ID NOS: 1, 3, and 5 encode polypeptides more closely related to each other than to human and chicken homooligomeric acetylcholine receptor nucleic acids. These data are unpersuasive because the analyzed sequences are limited to the most highly conserved regions of SEQ ID NOS: 1, 3, and 5, and not to the much longer, and less homologous, rejection may sequences set forth in the claims. Furthermore, attachment 1 is not part of a proper 1.132 Declaration, so it constitutes only hearsay and not persuasive evidence of the relatedness of SEQ ID NOS: 1, 3, and 5. Finally, as noted above, the specification fails to provide any guidance as to what sequence variants of SEQ ID NOS: 1, 3, and 5 will provide functional receptors, and which variants constitute loss of function mutations. Due to this element of unpredictability, and the large degree of variation in the claimed genus, one of skill in the art could not conclude that Applicant was in possession of the claimed genus at the time of filing.

Enablement

Claims 1-7, 10 and 34 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for nucleic acids which encode the polypeptides of SEQ ID NOS: 2, 4 and 6, does not reasonably provide enablement for a nucleic acids encoding a functional insect homooligomeric acetylcholine receptor as broadly claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

The claimed invention is a nucleic acid encoding a complete or partial insect acetylcholine receptor subunit having the ability to form functional homooligomeric acetylcholine receptors when expressed in host cells. The claims encompass all sequences which can hybridize under 2X SSC at 60°C to subsequences of SEQ ID NOS: 1, 3, and 5, as discussed above.

The specification and the prior art teach that the sequences of several vertebrate homooligomeric acetylcholine receptors were available at the time of filing. However, the specification fails to teach which amino acids are required for function, and which positions can tolerate substitutions. While it is known that many amino acid substitutions are generally possible in any given protein, certain positions in a polypeptide sequence are critical to the protein's structure/function relationship, such as various sites or regions where the biological activity resides or regions directly involved in binding, stability or catalysis, or which provide the correct three-dimensional spatial orientation for biologically active binding sites, or which

represent other properties or characteristics or properties of the protein. These or other regions may also be critical determinants of activity. These regions can tolerate only relatively conservative substitutions, or no substitutions. See Bowie et al (1990). The prior art teaches that the effects of amino acid substitutions and deletions on protein function were highly unpredictable. Rudinger (In Peptide Hormones J.A. Parsons, Ed. University Park Press, Baltimore, 1976, page 6) teaches that "[t]he significance of particular amino acids and sequences for different aspects of biological activity cannot be predicted *a priori* but must be determined from case to case by painstaking experimental study." Furthermore Ngo et al (In The Protein Folding Problem and Tertiary Structure Prediction, K. Merz Jr. and S. Legrand, Eds. Birkhauser, Boston, 1994, see page 492) teaches that "[i]t is not known if there exists an efficient algorithm for predicting the structure of a given protein from its amino acid sequence alone. Decades of research have failed to produce such an algorithm". Applicant has provided little or no guidance to enable one of skill in the art to determine, without undue experimentation, the positions in the claimed nucleic acids which are tolerant to change, and the nature and extent to of changes that can be made in these positions in order to retain function as required by the claims. Even if critical residues were identified in the specification, which they are not, the mere identification of these residues as critical would not be sufficient, as the skilled artisan would immediately recognize that critical sites must assume the proper three-dimensional configuration to be active, and that conformation is dependent on surrounding residues as well. Thus alterations in sequences which are not apparently part of a catalytic center or binding site can destroy activity

by altering the overall conformation of a protein.. One might argue that it would not be undue experimentation to express and assay polypeptides individually using the assays taught in the specification, and thereby empirically determine the function of each one. However as set forth in *In Re Fisher*, 166 USPQ 18(CCPA 1970), compliance with 35 USC 112, first paragraph requires:

> that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art; in cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and **their performance characteristics predicted by resort to known scientific laws**; in cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with the degree of unpredictability of the factors involved.

Emphasis added. The specification fails to provide any theoretical framework which can be used to accurately predict which amino acid substitutions will eliminate receptor function, and which will be tolerated as required by the claims. In the absence of such guidance, one of skill in the art would have to perform undue experimentation in order to make the invention commensurate in scope with the claims.

This rejection may be overcome by deleting from the claims embodiment (b).

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 10, 34, and 36 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 10, 34, and 36 are indefinite because they recite "the cell" without proper antecedent basis. The claims also lack any step in which the polypeptide is secreted into the culture medium, thus the polypeptide could not be isolated from the culture medium as recited.

Conclusion

Claim 35 is allowable. All claims are free of the art of record.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 703-306-5441. The examiner can normally be reached Monday through Friday between the hours of 6:20 AM and 3:50 PM. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John Leguyader, can be reached at 703-308-0447. The FAX numbers for art unit 1632 are 703-308-4242, and 703-305-3014. Additionally correspondence can be transmitted to the following RIGHTFAX numbers: 703-872-9306 for correspondence before final rejection, and 703-872-9307 for correspondence after final rejection.

Inquiries of a general nature or relating to the status of the application should be directed to the Patent Analyst Trina Turner whose telephone number is 703-305-3413.

Richard Schnizer, Ph.D.

JAMES KETTER
PRIMARY EXAMINER